ATTACHMENT - REMARKS

Claims 1-11 are pending in the present application. By this Amendment, Applicants have amended claim 5. Applicants respectfully submit that the present application is in condition for allowance based on the discussion which follows.

Claims 3-5 were rejected under 35 U.S.C. § 103(a) as being obvious over Bykov et al. (WO 02/24692) ("Bykov"), in view of Hartmann et al. (hereinafter "Hartmann").

As an initial point, Applicants gratefully appreciate the Examiner conducting a personal interview with their representative, Mr. Stephen Weyer, on August 5, 2008. In accordance with that interview, Applicants have amended claim 5 to further highlight distinctions between the present invention and that of the prior art. In particular, claim 5 has been amended to more clearly recite that the present treatment is directed to malignant melanoma cells producing inactive p53, which is inactive due to an "inactive conformation of p53." Thus, the presently claimed inactive p53, inactive due to an inactive conformation, is distinguishable from "mutant p53," as defined by Bykov.

Applicants respectfully submit that the present invention is not anticipated by or obvious in view of the prior art.

Bykov is directed to the use of various compounds which are able to reactivate the function of "mutant p53" proteins (Abstract). "Mutant p53" is unable to bind a specific DNA sequence necessary for p53 function. The loss of binding specificity for most "mutant p53" is due to point mutations in the core domain of p53 (residues 94-292) that harbors the specific DNA binding activity (Bykov, page 1, lines 11-23 and page 2, lines 19-22). Bykov is directed to reactivating "mutant p53" by restoring the

sequence-specific DNA binding activity to mutant p53 which, as noted above, has amino acid point mutations/substitutions.

In sharp contrast to Bykov, the present method is directed to treating malignant melanoma using the claimed compounds based on a new discovery that malignant melanoma cells produce a newly discovered "inactive" form of p53, i.e. "inactive p53," which is inactive due to a non-functional conformation (present specification, page 5, lines 1-15). More importantly, while "mutant p53," i.e. p53 with amino acid point mutations, are prominent in most human cancers, wild type p53 (i.e. active p53) is present in malignant melanoma (present specification, page 1, lines 17-23).

At the time the invention was made, it was known in the art that malignant melanoma were refractive to treatment by chemical drugs or radioactivity. In the art, it was also a commonly accepted fact that mutated p53 was not an important factor for the formation or emergence of malignant melanoma, although, as taught by, e.g., Hartmann, only a small fraction of melanoma patients carry mutated p53. Accordingly, it could be concluded that mutation of p53 is not necessary for the development of malignant melanoma, and thus that p53 inactivation is not likely to be biologically important for melanoma tumor progression. Logically, a treatment targeting p53 would not be expected to cure malignant melanoma. This latter conclusion is supported by the fact that malignant melanoma are notoriously resistant to chemotherapy, as well as radioactivity, since both of these treatments functionally involves activation of p53. Instead, melanoma respond to these treatments by upregulation of p53 expression, but without effect on tumor progression.

Based on the above commonly accepted fact that mutated p53 was not an important factor for the formation or emergence of malignant melanoma, there was no reason to believe, at the time the present invention was made, that a state-of-the-art method of treatment (such as taught by Bykov) would have any prospects of success if it would be applied to malignant melanoma. It is only through the work as outlined in the present specification that one of ordinary skill in the art would know to treatment malignant melanoma, as claimed. As will be apparent to one of ordinary skill in the art, cancers have various and differing characteristics and treatments vary greatly among different types of cancers. Therefore, unless there is a reasonably apparent reason why one of ordinary skill in the art would have been led to treat malignant melanoma from the prior art using the present method, the present method remains non-obvious in view of the prior art. The lack of a substantial amount of mutant p53 in malignant melanoma would not lead one to believe that the present method would be a beneficial treatment. Accordingly, Applicants respectfully submit that there would not have been any reasonably apparent reason why one of ordinary skill in the art would have been led to use the treatment disclosed in the prior art in a method for the treatment of malignant melanoma, as claimed.

Moreover, at the time the present invention was made, it was also a commonly accepted fact in the art that only about 10% of malignant melanoma human subjects have mutated p53. Accordingly, should the skilled person nevertheless, *arguendo*, contemplate applying the teachings of Bykov on malignant melanoma, *in spite of* (as asserted by the Applicants), or *motivated by* (as asserted by the Examiner) the teachings of Hartmann, he or she could, at best, in any case, would only expect a

maximum of 10% of the overall group of patients suffering from malignant melanoma to even stand a chance of being successfully treated by such method.

According to the findings of the present Applicants, it became evident that, in fact, 100% of the patients suffering from malignant melanoma could be treated according to the present invention, since the compounds (some of which have been previously used by Bykov for mutant p53) were also found to reactivate the inactivated conformation of wild type p53 discovered by the present inventors. The Applicants also found the inactivated conformation to be present in melanoma cells. Accordingly, this demonstrates an unexpected success.

Based on the foregoing, Applicants respectfully request that the rejection to claims 3-5 under 35 U.S.C. § 103(a) be withdrawn.

Claims 3-5 were rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,921,765, in view of Hartmann et al.

Applicants respectfully submit that claims 3-5, as currently pending, are not obvious in view of claims 1-2 of the '765 patent. The '765 patent is the U.S. national stage equivalent of Bykov. As discussed above with regard to Bykov, it would not have been obvious to one of ordinary skill in the art to treat malignant melanoma, as claimed, from the teaching of the '765 patent. While Applicants agree with the Examiner that malignant melanoma is a type of cancer, one of ordinary skill in the art would not have been led to treat malignant melanoma as a form of cancer from the '765 patent.

Based on the foregoing, Applicants respectfully request that the rejection to the claims, as being obvious in view of the '765 patent, be withdrawn.

Finally, claims 3-5 were rejected on the grounds of non-statutory obviousness-type double patenting, as being unpatentable over claims 1-2 of co-pending application 10/590,054 (hereinafter "the '054 application"), in view of Hartmann. As with the '765 patent, Applicants respectfully submit that it would not have been obvious to one of ordinary skill in the art to know to use the present method for the treatment of malignant melanoma from the '054 application. Nothing in the application or in the prior art would have led one to reasonably believe that the method disclosed in the '054 application would be effective for the treatment of malignant melanoma. Accordingly, one of ordinary skill in the art would not have been led to apply the teachings of the '054 application for the treatment of malignant melanoma, as claimed.

Based on the foregoing, Applicants respectfully request that the double patenting rejections to claims 3-5, in view of the '054 application, be withdrawn.

In view of the foregoing, Applicants respectfully submit that the present application is in condition for allowance.

Respectfully submitted,

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